REMARKS

This paper is filed in Response to the non-final Office Action mailed August 5, 2009. Claims 79, 95 to 105 are pending. New claims 106 to 124 have been added. Accordingly, upon entry of this paper, claims 79 and 95 to 124 are under consideration.

Regarding the New Claims

New claims 106 to 124 are supported throughout the specification. In particular, claims 106 to 120 are supported, for example, as described in the response filed October 8, 2008, with respect to new claims 80 to 94. New claims 121 to 123 are supported, for example, at page 13, lines 23-25, and as described in the response filed October 8, 2008, with respect to new claims 80 to 94. Claim 124, which parallels the language of claim 123 but recites the CM-1 antibody comprising the amino acid sequences of SEQ ID NO:1 and SEQ ID NO:3 is supported, for example, as described in the response filed October 8, 2008, with respect to new claims 80 to 94, and at page 15, lines 22-28. Thus, as claims 106 to 124 are supported by the originally filed specification, no new matter has been added and entry thereof is respectfully requested.

I. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The rejection of claims 79, 95 to 101 and 103 to 105 under 35 U.S.C. §112, first paragraph as allegedly lacking an adequate written description is respectfully traversed. According to the Patent Office, allegedly the claims lack support in the as-field specification (pages 2-5 of the Office Action).

Claims 79 and 95 to 124 are adequately described under 35 U.S.C. §112, first paragraph. Here, a proper analysis for written description under 35 U.S.C. §112, first paragraph is whether one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991); see, also, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). Possession is assessed from the viewpoint of one of ordinary skill in the art: "Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). The description needed to satisfy the requirements of 35 U.S.C. §112 "varies with the nature and scope of the invention at issue, and

with the scientific and technologic knowledge already in existence.....Since the law is applied to each invention in view of the state of the relevant knowledge, its application will vary with differences in the state of the knowledge in the field and differences in the predictability of the science...the law must take cognizance of the scientific facts." *Capon v. Eshhar*, 418 F.3d , 1349, 1357 (Fed. Cir. 2005), emphasis added. In sum, an adequate written description is a factual inquiry measured by one of ordinary skill in the art that varies with the nature and scope of the invention, taking into consideration the scientific and technologic knowledge in existence in the relevant field.

The law also does not require an actual reduction to practice or disclosure of a specific number of examples within the scope of the claims to satisfy the written description requirement under 35 U.S.C. §112, first paragraph. *In re Angstadt*, 537 F.2d 498, 502-503 (CCPA 1976), *Utter v. Hiraga*, 845 F.2d 993, 998-99 (Fed. Cir. 1988). In particular, "(1) examples are not necessary to support adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006). Consequently, actual reduction to practice is not required to satisfy written description under 35 U.S.C. §112, first paragraph.

Further in this regard, it is noted that *Enzo Biochem. V. Gen-Probe, Inc.*, 296 F.3d 1316 (Fed. Cir. 2002) is cited in the Action. However, in *Enzo II, i.e., Enzo V. Gen-Probe, Inc.*, 323 F.3d 956 (Fed. Cir. 2002) the Federal Circuit offered an example of a claim that would be adequately described by functional characteristics, namely "an isolated antibody capable of binding to antigen X....in light of the well defined structural characteristics of the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." Thus, under *Enzo II*, antibodies are adequately described solely by function and without any reference to a particular antibody sequence or structure, provided there is "disclosure of sufficient relevant identifying characteristics" of the antibodies, or where the antigen is fully characterized. Here, the claimed antibodies and functional fragments meet the standard set forth by the court in *Enzo II*, as corroborated by the more recent decision in *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052 (Fed. Cir. 2005)

In particular, the claimed antibodies and functional fragments bind to an epitope of an antigen that CM-1 antibody produced by a cell line deposited as DSM ACC 2584 binds, or comprising SEQ ID NOs:1 and 3 binds, and the antigen is expressed by at least one of five specifically recited human cell lines. Thus, the epitope of the antigen is defined in terms of 1) expression by at least one of five well defined human cell lines; and 2) binding to CM-1 antibody produced by cell line deposited as DSM ACC 2584, or comprising SEQ ID NOs:1 and 3. Thus, one of skill in the art would know, without having to know more about the identity of the epitope, antibodies and functional fragments within the scope of the claims. For example, competition binding is a simple and routine technique known in the art at the time of the invention to verify that a given antibody or functional fragment binds to an antigen expressed by a cell — an antibody or functional fragment that competes for CM-1 binding to an antigen expressed by at least one of the specifically recited cell lines would be within the scope of the claims, whereas an antibody that did not compete for CM-1 binding to antigen expressed by at least one of the specifically recited cell lines would not be within the scope of the claims. Consequently, one of skill in the art needs no more information about the epitope or antigen to which CM-1 binds in order to know antibodies and functional fragments within the scope of the claims.

Second, the claimed antibodies and functional fragments are described both functionally and structurally. In particular, as recited in the claims and discussed above, the claimed antibodies and functional fragments bind to an epitope of an antigen to which the CM-1 antibody binds when the CM-1 antibody is defined as either (1) an antibody produced by the cell line deposited as DSM ACC 2584, or (2) an antibody comprising SEQ ID NOs:1 and 3. Furthermore, members of antibody species that bind to a common epitope typically share sequence homology, such as in CDR3 of heavy chain variable region. Thus, antibodies that bind to the same epitope will be expected to inherently share sequence identity to SEQ ID NO:1 and/or SEQ ID NO:3. Further in this regard, antibodies and functional fragments of claims 106 to 123 specifically require at least a certain amount of sequence identity to SEQ ID NO:1 and/or SEQ ID NO:3. Thus, the claimed antibodies and functional fragments share a common functional (epitope binding) and structural (sequence identity) relationship with SEQ ID NO:1 and/or SEQ ID NO:3. Given the function and the sequence identity shared between the claimed

antibodies and functional fragments and SEQ ID NO:1 and/or SEQ ID NO:3, the antibodies and functional fragments have well defined functional and structural features in common.

Third, as previously pointed out in the record the knowledge and skill in the art in terms of antibody structure correlating with function at the time of the invention was high. Namely, the role of antibody heavy and light chain variable regions, particularly CDRs and FRs, in antigen binding was well understood by the skilled artisan at the time of the invention. The specification also discloses the role of antibody heavy and light chain variable regions in antigen binding (page 17, line 25, to page 18, line 10, and page 15, line 3). The role of variable region sequences, including CDRs in antigen binding was understood by the skilled artisan, and the position of CDRs in antibody variable regions can be predicted using techniques known in the art at the time of the invention (see, e.g., Morea et al., Methods 20:267 (2000)). Consequently, the level of knowledge and skill in the art with respect to antibody structure (CDRs, FRs, D- and J-regions, etc.) correlating with function was high at the time of the invention.

Fourth, because the knowledge and skill in the art in terms of antibody structure correlating with function was high and the predicted location and sequences of CDRs and FRs in SEQ ID NOs:1 and 3 that contribute to antigen binding would be known, the skilled artisan would also have known residues in SEQ ID NOs:1 and 3 amenable to substitution. For example, in view of the understanding of the role of CDRs and FRs in antigen binding at the time of the invention, the skilled artisan would know that an amino acid substitution, such as a conservative substitution, insertion or a deletion, for example, outside of a CDR or FR region of in SEQ ID NOs:1 and 3 would likely not destroy antigen binding activity. Furthermore, because the level of knowledge and skill in the art with respect to antibody structure correlating with function was high such that at the time of the invention one skilled in the art could have predicted with a high degree of confidence many substitutions of SEQ ID NOs:1 and 3 that would not destroy binding activity. Moreover, as evidenced by the previously submitted Declaration under 37 C.F.R. §1.132 executed by Dr. Peter Vollmers and Exhibits A-D, substitutions or deletions/insertions of a number of amino acids within antibody CDRs (i.e., CDR1, CDR2 or CDR3) and FRs can be well tolerated.

The facts of Applicants' claimed antibodies and functional fragments therefore are analogous to the facts in *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052 (Fed. Cir. 2005), in which the court held that a single embodiment of a protein (a reverse transcriptase

(RT)) provided an adequate written description for claims directed to a genus of such proteins since the single disclosed protein embodiment had 1) sufficient correlation between structure and function; and 2) shared significant homology with others. In affirming that the patent claims satisfied the written description requirement, as articulated in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (1997) and *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993), the court held that "the shared written description for the patents-in-issue recites both the DNA and amino acid sequences of a representative embodiment of the claimed RT enzyme. The specification also discloses test data that the enzyme produced by the listed sequence has the claimed features—DNA polymerase activity without RNase H activity. Under both the *Eli Lilly* and *Fiers* analysis, the specification at bar is sufficient. In short, there is no error in the district court's ruling that the claims in the patents-in-suit satisfy the written description requirement of §112." Thus, the claims of the patents-in-issue in *Invitrogen*, which did not recite in the claims a particular amount of sequence homology or identity to the reference sequence, satisfied the written description requirement even though there was only a single disclosed embodiment in the specification. In view of *Invitrogen*, a single embodiment provides an adequate written description of a genus of proteins where there is sufficient correlation between protein structure and function, and the members of the species share significant homology.

Here, given the substantial understanding of antibody structure correlating with function at the time of the invention, and that the specification discloses light and heavy chain variable region sequences and in view of the knowledge in the art such that one of skill in the art could have predicted the location and sequences of all CDRs and the location and sequences of all FRs, amino acids that mediate antigen binding. The claimed antibodies and functional fragments also share common structural (sequence homology) and functional (bind to the epitope to which the CM-1 antibody, which either is produced by a cell line deposited as DSM ACC 2584 or comprises SEQ ID NOs:1 and 3, specifically bind) attributes. Consequently, the facts of the claims under consideration closely parallel the facts in the *Invitrogen* decision.

The Patent Office cites *In re Alonso*, 545 F.3d 1015 (Fed. Cir. 2008) to support the rejection. However, *In re Alonso* is inapposite to the claims of this application because the facts and context underlying the claims under consideration are highly distinguishable from those that led to the *In re Alonso* decision, and are instead analogous to the facts in the *Invitrogen* decision as discussed above.

First, the *Alonso* claims are directed to methods of treating neurofibrosarcomas, using antibodies idiotypic to the neurofibrosarcomas. Significantly, the antibodies in *Alonso* were not limited to binding to any particular epitope or even any particular antigen. Instead, the genus of antibodies encompassed by the *Alonso* claims could bind to any epitope and any antigen expressed, which epitopes and antigens had different and unknown specificities. Thus, the claimed treatment methods of *Alonso* encompassed antibodies not limited to binding to any particular epitope or any particular antigen.

In contrast to the antibodies of *Alonso*, the claimed antibodies and functional fragments all specifically bind to a single epitope, namely the epitope of an antigen expressed by at least one of five well defined neoplastic human cell lines recited in the claims where that epitope is the epitope to which the CM-1 antibody specifically binds. Also in contrast to *Alonso*, the claimed antibodies and functional fragments bind to a polypeptide expressed by at least one of five well defined deposited human cell lines, namely HT-29 (ATCC Accession No. HTB-38; DSMZ Accession No. ACC 299), CACO-2 (ATCC Accession No. HBT-37; DSMZ Accession No. ACC 169), COLO-320 (DSMZ Accession No. ACC 144), COLO-206F (DSMZ Accession No. ACC 21), or COLO-678 (DSMZ Accession No. 194) cells.

Second, the antibodies in *Alonso* were not defined by or limited to any structure. In contrast to the *Alonso* antibodies, the claimed antibodies and functional fragments share a common structure due to 1) binding to the same epitope; and 2) claims 106 to 123 specifically recite various amounts of sequence identity to light and/or heavy chain variable regions (SEQ ID NOs:1 and 3). Thus, the claimed antibodies and functional fragments share a common structure (amino acid residues) owing to binding to the same epitope, and as specifically recited in claims 106 to 123.

The relevance of such claimed structure is illustrated by Xu and Davis (Immunity 13:37 (2000)), submitted herewith as Exhibit 1, who reported that CDR3 of the heavy chain variable region was the primary determinant which confers antigen recognition and specificity. Consequently, the claimed antibodies and functional fragments will have a CDR3 heavy chain variable region with significant sequence identity to CDR3 of SEQ ID NO:3, whereas in the *Alonso* antibodies there was no structural relationship among the genus of antibodies.

Third, the patent application at issue in *Alonso* (USSN 08/469,749) claimed priority to an application filed in 1988. In contrast, the subject application claims priority to an applications

filed March, 2002, which is at least 13 years after the *Alonso* priority application was filed. Obviously, the state of knowledge in the art concerning antibody structure correlating with function was greater in 2002 than in 1988. Indeed, the state of the art was so much more advanced in 2002 that a finding based upon the state of the art in 1988 is wholly insufficient to make a factual evaluation of an invention in 2002. As an example of the advanced state of the art, in 1992, a publication reported substitutions of framework residues of humanized antibodies with donor framework residues improved antibody affinity (Foote and Winter, J. Mol. Biol. 224:487 (1992), submitted herewith as Exhibit 2) indicating that FR residue substitutions are tolerated and can improve affinity. As another example of the advanced state of the art, two publications, in 1998 and 2000, reported that CDR3 of heavy chain variable region was the principal determinant of antigen recognition and specificity (Exhibit 1; see, also, Morea et al. J. Mol. Biol. 275:269 (1998), submitted herewith as Exhibit 3). In particular, the authors of Exhibit 1 reported that changes in heavy chain CDR3 amino acids accounted for the diversity of response against various protein antigens, and did not require changes to CDR1 or CDR2 sequences, indicating that one of skill in the art would know that heavy chain CDR1 and CDR2 are less important for antigen specificity compared to heavy chain CDR3. As yet another example of the advanced state of the art, a review publication by Padlan (Molecular Immunology 31:169 (1994), submitted herewith as Exhibit 4) report the role of FRs and CDRs in antibody function, that FRs have conserved substitutions (e.g., page 177), that CDR3 has a primary role in antigen specificity (page 196 second column), and that particular amino acid residues are more prevalent in CDRs/FRs (pages 197-198). Still another publication evidencing the advanced state of the art reported the construction of a fully human combinatorial antibody library based upon human consensus FRs and CDRs (Knappik et al., J. Mol. Biol. 296:57 (2000) submitted herewith as Exhibit 5). Consequently, one of skill in the art would know antibody sequence regions more or less amenable to substitution, the types of amino acid residues that are most prevalent and/or tolerated at given positions and could therefore deduce functional variants based upon this knowledge.

A further example of the advanced state of the art is a publication by Collet *et al.* (Proc. Nat'l. Acad. Sci. USA 89:10026 (1992), submitted herewith as Exhibit 6), who reported that heavy chain variable region sequences could productively pair with a variety of different light chain variable region sequences and maintain antigen binding specificity (see, e.g., abstract, a

heavy chain could productively pair with a light chain and still maintain HIV gp120 antigen binding activity from 43% -100%). Even unrelated light chain variable region sequences (to tetanus toxoid) productively paired with a heavy chain variable region sequence (to HIV gp120) to produce an antibody that maintained binding to HIV gp120 with a high degree of frequency (page 10029-10030). Thus, one of skill in the art would have known that the heavy chain variable region sequence can productively pair with a number of light chain variable region sequences and retain antigen specificity, indicating that variations to the light chain variable region sequence are tolerated.

Thus, the knowledge in the art concerning antibody structure correlating with function was significantly greater in 2002 than in 1988. Consequently, in view of the high level of knowledge and skill in the art, one of skill in the art would have been able to reasonably predict with a high degree of confidence variants of SEQ ID NO:1 and 3 that would retain binding.

Furthermore, in view of the fact that the claimed antibodies and functional fragments specifically bind to a single epitope and share a common structure, unlike the *Alonso* antibodies, and that the state of the art at the time that the application was filed in 2002 was more advanced as compared to the state of the art of the application at issue in *Alonso*, the claims under consideration are highly distinguishable from the *Alonso* decision.

Lastly, but significantly, the Appellants in the *Alonso* decision failed to timely present the argument that the neurofibrosarcoma antibodies were adequately described in view of the well-known correlation between structure and function of antibodies. Thus, the *Alonso* court expressly did not consider the merits of this argument since it was not raised during proceedings before the Board. Consequently, given the fact that arguments pointing out the well-known correlation between structure and function of antibodies were not considered by the *Alonso* court, the *Alonso* decision does not stand for the proposition that antibodies are not adequately described in spite of the well-known correlation between structure and function of antibodies, particularly given the advances in the state of the art in the 14 years after the *Alonso* priority application was filed.

In sum, a proper analysis of the description requirement under 35 U.S.C. §112, first paragraph, requires a factual inquiry and consideration of the state of the knowledge in the relevant field. Here, the facts of the claimed antibodies and functional fragments are readily distinguishable from *Alonso*. Namely, unlike *Alonso*, the claimed antibodies and functional

fragments 1) specifically bind to a single epitope expressed by at least one of five well-defined deposited human cell lines; 2) share a common sequence structure due to binding to a single epitope and as specifically recited in claims 106 to 123; and 3) unlike *Alonso*, the knowledge in the art concerning antibody structure correlating with function was far more advanced in 2002 than in 1988, the priority date of the *Alonso* application. Furthermore, in reaching its decision the *Alonso* court failed to consider the well-known correlation between structure and function of antibodies.

Additionally, the Declaration under 37 C.F.R. §1.132 executed by Dr. Peter Vollmers, and corroborating Exhibits A-D previously filed on April 16, 2008, verifies that the claims are adequately described under 35 U.S.C. §112, first paragraph. In the previously filed Declaration, Dr. Vollmers provided objective facts, and conclusions based upon the objective facts, with corroborating Exhibits A-D in the Declaration, that the skilled artisan would readily envision antibodies with 75% or more identity to SEQ ID NO:1 or 3, as well as antibodies having certain types of amino acid substitutions, that would retain at least partial binding activity (see, for example, paragraphs 11 and 20).

In sum, given the totality of: (1) guidance in the specification and the high level of knowledge and skill in the art with respect to antibody structure correlating with function at the time of the invention, (2) knowledge of the heavy and light chain variable region sequences (SEQ ID NOs:1 and 3) and the CDRs and FRs that confer binding, and (3) the previously filed Declaration under 37 C.F.R. §1.132 executed by Dr. Vollmers and Exhibits A-D, the skilled artisan would know of general regions and particular residues that would be amenable to variation, and would therefore be apprised of a number of sequence variants of SEQ ID NOs:1 and 3 having binding activity, and therefore the claims meet the written description standard articulated by the court in *Invitrogen*. Further, in view of the substantially greater understanding of antibody sequence structure and correlation with function in 2002 compared to 1988, and the fact that the claimed antibodies and fragments will bind to a single identical epitope, namely the epitope to which the CM-1 antibody, produced by a cell line deposited as DSM ACC 2584 binds or comprising SEQ ID NOs:1 and 3, binds, and will also necessarily have sequence homology with SEQ ID NOs:1 or 3, the facts of the claims under consideration are clearly distinguishable from the facts in *Alonso*. Consequently, the claims are adequately described under 35 U.S.C. §112, first paragraph, and the rejection must be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that the pending claims clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 33975.

Respectfully submitted,

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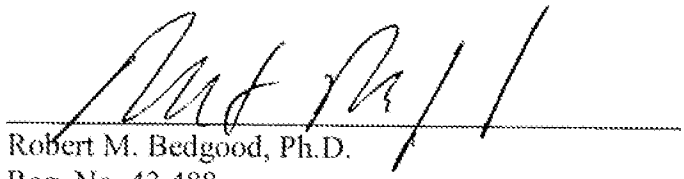
Date: December 4, 2009



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